Selective Ortho C−H Activation of Haloarenes by an Ir(I) System

Eyal Ben-Ari,[†] Mark Gandelman,[†] Haim Rozenberg,[‡] Linda J. W. Shimon,[‡] and David Milstein*,[†]

Departments of Organic Chemistry and Chemical Services, The Weizmann Institute of Science, Rehovot 76100, Israel

The selective activation of strong C−H bonds in the presence of *substitutionally reactive* groups, such as halo-substituents, is important for synthetic applications. Recent examples of C−H activation in haloarenes by soluble transition metal complexes were reported.[1] Because of steric reasons, activation of the less hindered meta or para C−H bonds in haloarenes was observed. Activation of the ortho C−H bond is desirable since it may lead to the functionalization of haloarenes in the most sterically hindered position.[2] Here we report on an electron-rich cationic Ir(I) system which undergoes facile arene C−H bond activation, leading with benzene to a crystallographically characterized, unsaturated, stable Ir(III) hydridophenyl complex. Remarkably, this system exhibits *unprecedented regioselectivity* toward ortho-C−H bond activation in chloro- and bromobenzene, utilizing the halogen as a directing group.

We have recently reported electron-rich, neutral iridium complexes of 2,6-bis-(di-*tert*-butyl phosphino methyl)pyridine (PNP).[3] When the *cationic* PNP−Ir(I) complex **1**[4] was dissolved in benzene, quantitative C−H activation took place, yielding the iridium phenyl hydride complex **2** within 48 h at 25 °C or 1 h at 60 °C (Scheme 1). $^{31}P\{^1H\}$ NMR of **2** in CD_2Cl_2[4] exhibits a doublet at 54 ppm and ^1H NMR reveals a highfield shifted triplet at −44 ppm, characteristic of a hydride *trans* to a vacant coordination site,[5] indicating a square pyramidal geometry.

The X-ray structure of **2**[4] reveals that the iridium atom is located in the center of a slightly distorted square pyramid with the hydride positioned *trans* to the vacant site (Figure 1).

Complex **2** does not decompose upon heating to 100 °C for 24 h in the solid state or in a benzene solution, representing a rare example of a thermally stable coordinatively unsaturated M(III) d^6 hydridoaryl complex. Unsaturated hydridoaryl complexes were postulated as key intermediates in catalytic processes such as hydroarylation of alkenes[2] and decarbonylation of aldehydes[6] although not observed in either case. Interestingly, Goldman reported recently the neutral, isoelectronic, thermally unstable five-coordinate (PCP)Ir−hydridophenyl complex[7] (PCP = η^3-2,6-($^tBu_2$-$PCH_2)_2C_6H_3$) which was characterized in solution at low temperature. Werner reported the thermally stable $Ir(P^iPr_3)_2(H)(Ph)(Cl)$,[8] which is the only crystallographically characterized unsaturated Ir(H)(R) (R = alkyl, aryl) complex. This trigonal bipyramidal complex is stabilized by strong π-donation of the chloride ligand to an empty d-orbital of the metal. Complex **2** lacks such stabilization. We believe that it is the first crystallographically characterized square pyramidal iridium hydrido-aryl (or -alkyl) complex.[9] Square pyramidal d^6 PCP complexes are common.[10]

Although stable, complex **2** exhibits arene exchange reactivity. When a slurry of **2** in C_6D_6 was heated at 50 °C, disappearance of the hydride and phenyl signals was observed in the ^1H NMR, while the ^{31}P NMR remained unchanged.
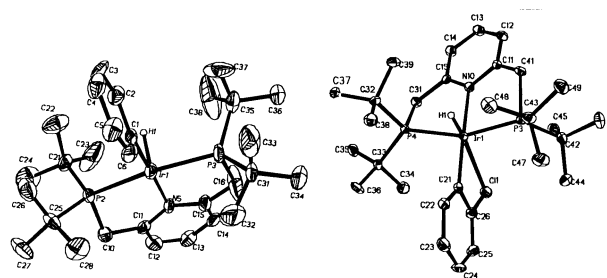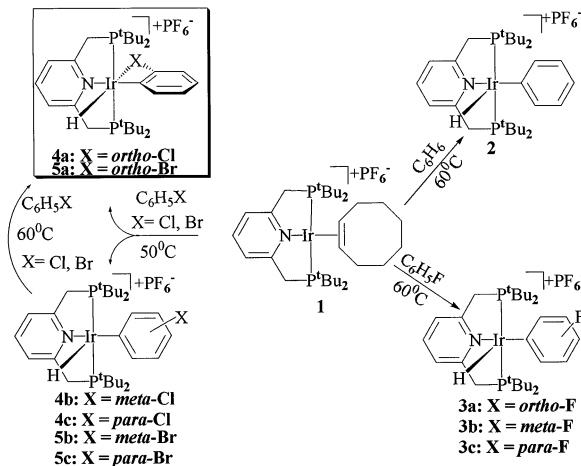
Figure 1. ORTEP drawings of **2** (left) and **4a**. Hydrogen atoms (except hydride) and hexafluorophosphate counterion were omitted for clarity. Selected bond lengths (Å) and angles (deg): **2:** Ir(1)−N(5) 2.142(5), Ir(1)−C(1) 2.043(7), Ir(1)−H(1) 1.66(7), C(1)−Ir(1)−H(1) 88, N(5)−Ir(1)−H(1) 94. **4a:** Ir(1)−C(21) 2.045, Ir(1)−Cl(1) 2.816, C(26)−Cl(1) 1.78, Ir(1)−Cl(1)−C(26) 72, Cl(1)−C(26)−C(21) 63.

Scheme 1

Formation of $(PNP)Ir(D)(C_6D_5)$ was confirmed by ^2H NMR. As shown recently by Goldman, such an intermolecular arene exchange in the unstable PCP-based Ir(H)(Ph) system takes place rapidly at low temperature and follows a dissociative mechanism.[7] It is likely that the arene exchange in the case of **2** requires heating to overcome the barrier of C−H reductive elimination.

2 and (PCP)Ir(H)(Ph) represent a rare case of a differently charged, isoelectronic couple of the same metal that undergoes C−H reductive elimination/oxidative addition. A comparison of the CO absorption frequency of (PCP)Ir(H)(Ph)CO (1973 cm^{-1})[7] and that of **2**−CO (2005 cm^{-1}; H *trans* to CO in both cases)[4] indicates that the electron density at the metal center in the cationic Ir(III) complex is lower, as expected. The reasons for the higher stability of **2**, which seems counterintuitive, are being explored.[11]

Complex **1** activates C−H bonds of aryl halides with not even traces of C-halide oxidative addition products, even with bromobenzene (vide infra). When **1** was heated in fluorobenzene at 50 °C, three Ir−hydridoaryl complexes were formed and characterized by

NMR as ortho-, meta-, and para-activated (PNP)Ir(H)(C$_6$H$_4$F) (**3a**–**c**, respectively), in a ratio of **3a**:**3b**:**3c**, 2:2:1, indicating lack of any selectivity in C–H activation.

In contrast, complex **1** reacts with chlorobenzene at 50 °C with preference to the ortho position, yielding the ortho-, meta-, and para-C–H activated complexes **4a**–**c** in a ratio of 4.6:2:1, respectively, at the point when **1** has completely disappeared. Monitoring the reaction by NMR revealed that at 10% conversion the ratio o/m/p was 4:2:1.[4] Remarkably, continued heating of this mixture at 60 °C after consumption of **1** results in clean conversion of **4b** and **4c** to the ortho-activated **4a** as the only product. Most likely, competitive reversible formation of **4b** and **4c** and irreversible formation of **4a** are involved. These results clearly indicate that **4a** is thermodynamically and kinetically favored despite the steric hindrance imposed by the chlorine atom.

Interestingly, whereas the hydride ligands of **4b** and **4c** exhibit in the ^{1}H NMR spectrum signals at −41 ppm and −42 ppm, respectively, indicating a vacant site *trans* to the hydride, the hydride of **4a** appears at −33 ppm, which is characteristic of M–H *trans* to an occupied coordination site. This indicates that the chlorine atom of **4a** is coordinated to the Ir center and is located *trans*- to the hydride, as confirmed by X-ray (vide infra). The intramolecular coordination of Cl explains the higher thermodynamic stability of **4a** relative to **4b,c** where such coordination is obviously impossible.

It is known that the ortho positions in haloarenes are the most acidic ones, especially in fluoroarenes.[12] Indeed, Caulton showed that an Os(II) complex activates preferentially the o-C–H bonds in fluoroarenes although no interaction between fluorine and the metal was found.[5b] As explained, this is a result of the preference of Os for interaction with the π-cloud ortho to the C–F bond, making the ortho activation kinetically favored. Such arguments are unlikely to be important in the case of the PNP–Ir system, as the reaction of **1** with fluorobenzene results in a statistical mixture of C–H cleaved products. Therefore, we conclude that the ortho C–H activation in chlorobenzene is directed by pre-coordination of the chlorine atom to iridium. Halocarbon coordination to transition metals is well documented,[13] although examples of chloro- and bromoarene coordination are not common.[13,14] As shown experimentally[13,15] and theoretically,[15] due to the significant p-character of the halide donor orbital, the M–X–C (X = halide) angles in halocarbon complexes must be close to 90−100°. Such coordination of the haloarene to the PNP–Ir system will place the ortho C–H bond in proximity of the metal, resulting in kinetically favored insertion of the iridium center into this bond.

A single-crystal X-ray analysis of **4a**[4] reveals that the Ir atom is located in the center of a distorted octahedron (Figure 1). The chlorine atom is coordinated to the metal and, as predicted from the NMR data, it is located *trans* to the hydride. Although the Ir–Cl bond length of 2.816 Å is significantly shorter than the sum of van der Waals radii of Ir and Cl atoms, it is longer than other reported Ir–Cl bonds in coordinated chloroalkanes.[13] This elongation is probably due to some strain in the four-membered ring, as indicated by the 72° angle of Ir–Cl–C. Noteworthy, the C–Cl bond (1.781 Å) is significantly elongated compared to the one in free C$_6$H$_5$Cl (1.700 Å),[16] suggesting π-back-donation from a filled metal d-orbital to the empty C–Cl σ*-orbital. Cl Coordination makes **4a** the thermodynamically favored product.

Reaction of **1** with C$_6$H$_5$Br is similar to that of C$_6$H$_5$Cl, yielding the ortho-, meta-, and para-C–H activated complexes **5a**–**c** at 50 °C in a ratio of 7:2:1, respectively, at the point when **1** has completely disappeared. Continued heating at 60 °C results in the quantitative formation of **5a** as the only product,[4] indicating that it is kinetically and thermodynamically favored.

The observed statistical C–H activation with C$_6$H$_5$F and the selective C–H cleavage with C$_6$H$_5$Cl and C$_6$H$_5$Br, directed by halogen coordination, is consistent with the ligating ability F ≪ Cl < Br. To our knowledge, this is the *first example of selective ortho C–H bond activation of haloarenes in solution*.[17] Usually, C–H bond activation in haloarenes takes place at the less hindered positions, resulting predominantly in a mixture of meta- and para-activated complexes.

In conclusion, a PNP-based cationic iridium(I) system exhibits high activity and selectivity in aromatic C–H activation. A stable square pyramidal Ir–hydridophenyl complex was crystallographically characterized. Unprecedented selective ortho C–H activation of haloarenes was achieved, the process being directed by halogen coordination, and being thermodynamically and kinetically favorable.

Supporting Information Available: Experimental procedures and characterization of complexes **2**–**6** (PDF) and X-ray data for **3** and **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305. (b) Tellers, D. T.; Yung, C. M.; Arndtsen, B. A.; Adamson, D. R.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 1400. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (d) Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330.

(2) Examples of ortho-directed C–H activation by substitutionally stable groups are known, most notably Murai's keto-directed catalytic ortho functionalization: Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826 and references therein.

(3) Hermann, D.; Gandelman, M.; Rozenberg, H.; Shimon, L. J. W.; Milstein, D. *Organometallics* **2002**, *21*, 812.

(4) See Supporting Information.

(5) (a) Moulton, C. J.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1976**, 1020. (b) Renkema, K. B.; Bsque, R.; Streib, W.; Maseras, F.; Eisenstein, O.; Caulton, K. G. *J. Am. Chem. Soc.* **1999**, *121*, 10895.

(6) Doughty, D. H.; Pignolet, L. H. *J. Am. Chem. Soc.* **1978**, *92*, 2, 7083.

(7) Kanzelberger, M.; Singh, B.; Czerw, M.; Krogh-Jepersen, K.; A. S. Goldman, *J. Am. Chem. Soc.* **2000**, *122*, 11017.

(8) Werner, H.; Höhn, A.; Dziallas, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *12*, 1090.

(9) A closely related crystallographically characterized square pyramidal complex L$_2$Os(CO)(H)(C$_6$H$_3$F$_2$) was reported: see ref 5b

(10) For example: (a) Rybtchinski, B.; Vigalok, A.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **1996**, *118*, 12406. (b) Gandelman, M.; Vigalok, A.; Shimon, L. J. W.; Milstein, D. *Organometallics* **1997**, *16*, 3981.

(11) Reductive C–H addition is unlikely since (PNP)Ir(I)$^+$ has a higher electron density at the metal center than **2**: the CO absorption of (PNP)IrCO$^+$ (1964 cm^{-1}) is at a lower frequency than that of **2**–CO: Ben Ari, E.; Gandelman, M.; Milstein, D. To be published. For a study on the effect of metal oxidation state on C–H activation, see: Krogh-Jespersen, K.; Czerw, M.; Summa, N.; Renkema, K. B.; Achord, P. B.; Goldman, A. S. *J. Am. Chem. Soc.* **2002**, *124*, 11404. Oxidative vs reductive additions are discussed in: Crabtree, R. H.; Quirk, J. M. *J. Organomet. Chem.* **1980**, *199*, 99.

(12) Schlosser, M.; Marzi, E.; Cottet, F.; Büker, H. H.; Nibbering, N. M. M. *Chem. Eur. J.* **2001**, *7*, 3511.

(13) Kulawiec, R. J.; Crabtree, R. H.; *Coord. Chem. Rev.* **1990**, *99*, 89.

(14) (a) Butts, M. D.; Scott, B. L.; Kubas, G. J. *J. Am. Chem. Soc.* **1996**, *118*, 1970. η^1 coordination of chlorobenzene: (b) Korolev, A. V.; Delpech, F.; Dagorne, S.; Guzei, I. A.; Jordan, R. F. *Organometallics* **2001**, *20*, 3367 (c) Kowalczyk, J. J.; Agbossou, S. K.; Gladysz, J. A. *J. Organomet. Chem.* **1990**, *397*, 333.

(15) (a) M. D.; Scott, B. L.; Kubas, G. J. *J. Am. Chem. Soc.* **1996**, *118*, 11831 (b) Ortiz, J. V.; Havlas, Z.; Hoffmann, R. *Helv. Chim. Acta* **1984**, *67*, 1. (c) Czech, P. T.; Gladysz, J. A.; Fenske, R. F. *Organometallics* **1989**, *8*, 1806.

(16) *Handbook of Chemistry and Physics*, 57th ed.; CRC Press: Cleveland, OH, 1976−1977.

(17) Competitive ortho C–H and ipso C–Cl bond activation of chlorobenzene by FeO$^+$ in the gas phase was reported: Brönstrup, M.; Trage, C.; Schröder, D.; Schwartz, H. *J. Am. Chem. Soc.* **2000**, *122*, 699.

JA028362P